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Do complications of pancreatic cancer surgical treatment change in the aging world?

The effect of age on pancreatic surgery complications

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Abstract

Aim: The elderly population in the community population is increasing day by day. Pancreatic malignancies have poor survival and high mortality and morbidity rates. In our study, we aimed to evaluate the effect of age on pancreaticoduodenectomy surgery.

Material and Methods: Patients who underwent pancreaticoduodenectomy between 2012 and 2020 were divided into 3 groups according to their age (60 years and younger group 1, 60-80 years old group 2, 80 years and older group 3). Early mortality and morbidity outcomes between the groups were compared.

Results: Parallel to the increase in age, a statistically significant increase was found in the ASA score (p:0.000), length of stay in the intensive care unit (p:0.021), mortality (p:0.003) and morbidity (p:0.021) rates between the groups.

Discussion: Considering the increasing elderly population in the world, we found that surgical intervention such as pancreaticoduodenectomy with high comorbidity can be performed with higher mortality and morbidity risks compared to younger patients.

Keywords
Pancreas Cancer, Pancreaticoduodenectomy, Mortality, Morbidity, Age

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Introduction

The number of elderly people in the population of the society is increasing day by day [1]. While the proportion of the elderly population in the total population is 9.5% in 2020, this situation is expected to increase to 16.3% in 2040 and 22.6% in 2060 [2]. There is a parallelism between the increase in life expectancy and the incidence of cancer. It is predicted that by 2035, 14 million new cancer cases will be detected, constituting almost 60% of the global cancer incidence [3]. It is estimated that pancreatic cancer, which is in the 4th place in cancer-related deaths today, will rise to the second place in cancer-related deaths by 2030 [4].

Despite advances in the diagnosis and treatment of pancreatic cancer, the 1-year survival rate is 24% [5]. While the 5-year survival rate is reported as 5% in patients with successful surgical resection, the median survival in locally advanced or metastatic disease is 6-11 and 2-6 months, respectively [6]. In addition, pancreaticoduodenectomy operations for pancreatic cancer have a morbidity rate of 40-50% and a mortality rate of 1-3%, even in experienced centers [7]. In elderly patients, pancreatic cancer is associated with higher perioperative mortality and morbidity rates, higher need for intensive care unit stay, and higher hospital readmission rates [8].

The increase in the average life expectancy, the increase in the incidence of pancreatic cancer with age, and the high mortality and morbidity of pancreatic surgery have made pancreatic surgery in elderly patients a contradiction. In our study, we aimed to evaluate the effect of advanced age on morbidity and mortality in pancreaticoduodenectomy operations.

Material and Methods

This retrospective study was conducted with the approval of the Institutional Review Board No. 2021-056. All study procedures were performed in accordance with local ethical standards and with the 1964 Helsinki Declaration and its amendments.

Patient selection and groups

The data of patients who underwent pancreaticoduodenectomy for a mass located in the head of the pancreas between 2012 and 2020 were reviewed retrospectively. Patients who did not receive neoadjuvant therapy, did not undergo portal vein resection and whose pathology results were adenocarcinoma were included in the study. The patients were divided into 3 groups according to their age. They were grouped as 60 years old and below, 60-80 years old and 80 years old and above. Patients aged 60 and below were named group 1, patients aged 60-80 years were named group 2, and patients aged 80 and over were named group 3.

Patients' ages, genders, ASA (American Society of Anesthesiologists) scores, postoperative complications, early mortality, and length of stay in the service and intensive care unit were recorded. The most important parameter was postoperative complications, which were classified according to Clavien and Dindo. Those who died during hospitalization or within the first 30 days after discharge were considered as early mortality. Secondly, hospitalization times (intensive care and service times separately) and postoperative pathological stages were compared between the groups.

Preoperative preparation, surgical technique and postoperative follow-up

Nutritional support was started for patients with low preoperative albumin value and it was aimed to have an albumin value of 3 g/dl and above. Preoperative low molecular weight heparin (1mg/kg Enoxaparin Sodium) was started in all patients, and prophylaxis was administered with preoperative 1st generation cephalosporin (Cefazolin 30mg/kg) to patients who did not receive routine antibiotherapy.

All patients were operated by the same experienced surgeons. Anastomosis type was preferred according to the characteristics of the pancreatic tissue and duct. The main bile duct was anastomosed to the jejunum with intermittent or continuous suture techniques. The pylorus was not preserved in all patients, and Braun anastomosis was added after gastrojejunostomy anastomosis.

Postoperatively, all patients were followed up according to a standard procedure. On the 1st, 3rd and 5th days, drain amylase was studied from both drains and leak staging was performed as defined by the pancreatic leak group in 2016 [9]. Oral feeding was started on the 3rd day in all patients who did not show any leakage. Antibiotics other than those recommended by infectious diseases were not given during discharge, and nutritional support with low molecular weight heparin was given to all patients.

Statistical analysis

The data were analyzed using SPSS software, version 23 (Chicago, IL). Descriptive data were expressed as mean±SD and compared using the one-way ANOVA. Categorical variables were expressed as percentages and compared using the Chi-square test. A p-value <0.05 was considered statistically significant.

Results

The data of all 153 patients who underwent pancreaticoduodenectomy in our clinic between 2012 and 2020 were reviewed retrospectively. The mean age of the patients was 65.7±12.2 years. Of the patients, 85 (55.6%) were male and 68 (44.4%) were female. The mean hospitalization day in the intensive care unit was 3.95±5.46 days, and the total hospitalization time (service and intensive care unit) was 12.89±8.13 days. When the ASA scores were evaluated, 38 (24.8%) of the patients were ASA I, 74 (48.4%) ASA II, 41 (26.8) ASA III. The morbidity assessment of the patients was performed according to the Clavien Dindo classification. Delayed gastric emptying (DGE), post-pancreatectomy hemorrhage, and POPF were classified based on the International Study Group of Pancreatic Surgery definitions [10-12]. Pancreatic fistula with antibiotic revision, wound infection, gastric emptying difficulty that did not require endoscopic intervention, respiratory distress that regressed with medical treatment, ileus that did not require postoperative surgical intervention, bleeding that did not require surgical or radiological interventional procedures, constituted Class II complications. In the treatment of these complications, if endoscopic, interventional or surgical intervention was required, it was noted that these patients had class 3 complications. It was noted that patients with organ

Table 1. Comparison of demographic data and results between groups

	Group 1	Group 2	Group 3	Totaly	P- value
	N:47(30,7%)	N:82(53,6%)	N:24(15,7%)	N:153	
Age	51,6±7.27	68,6±5,3	83,5±3,1	65,7±12,2	0
Gender					
Male	24 (51,1%)	49 (59,8%)	12 (50%)	85 (55,6%)	0,53
Female	23 (48,9%)	33 (40,2%)	12 (50 %)	68 (44,4%)	
IC Hospitalization day	2,96±5,12	3,72±4,81	6,67±7,31	3,95±5,46	0,021
Total hospitalization day	11,09±6,85	13,76±8,62	13,46±8,45	12,89±8,13	0,187
ASA					
1	38 %80,9	0	0	38 %24,8	0.000
2	9 %19,1	64 %78,0	1 %4,2	74 %48,4	
3	0	18 %22,0	23 %95,8	41 %26,8	
Morbidity					
No	31 %66,0	39 %47,6	8 %33,3	78 %51,0	0,021
Clavien Dindo 2	8 %17,0	26 %31,7	6 %25,0	40 %26,1	
Clavien Dindo 3	3 %6,4	4 %4,9	0	7 %4,6	
Clavien Dindo 4	0	1 %1,2	0	1 %0,7	
Clavien Dindo 5	5 %10,6	12 %14,6	10 %41,7	5 %17,6	
Mortality	5 %10,6	12 %14,6	10 %41,7	27 %17,6	0,003
Stage					
1	15 %31,9	27 %32,9	5 %20,8	47 %30,7	0,592
2	20 %42,6	30 %36,6	10 %41,7	60 %39,1	
3	11 %23,4	25 %30,5	9 %37,5	45 %29,4	
4	1 %2,1	0	0	1 %0,7	

IC: Intensive Care, ASA: American Society of Anesthesiologists

Table 2. Causes of mortality in the groups

Cause of mortality	Group 1 (n:5)	Group 2 (n:12)	Group 3 (n:10)
Pancreatic fistula	4 (80%)	7 (58.4%)	6 (60 %)
Respiratory Failure		2 (16.7%)	2 (20%)
MI			1 (10 %)
Bleeding		1 (8.3%)	
Bile fistula		1 (8.3%)	
Abdominal sepsis	1 (20%)	1 (8.3%)	1 (10 %)

MI: Myocardial Infarction

failure had 4th class complications, and those who lost their lives during hospitalization or within the first 30 days after discharge due to postoperative complications were 5th class complications. Mortality was detected in 27 (17.6%) of the patients.

The patients were divided into 3 groups according to their age. Group 1 consisted of patients aged 60 years and younger (n:47, 30.7%), group 2 patients aged 60-80 years (n:82, 53.6%), group 3 patients aged 80 years and older (n: 24, 15.7%). The mean age was 51.6±7.27 years in the 1st group, 68.6±5.3 years in the 2nd group and 83.5±3.1 years in the 3rd group, and it was statistically significant (p:0.000). In the gender evaluation between groups, 24 (51.1%) of group 1 were male and 23 (48.9%) were female. In Group 2, there were 33 men (40.2%), 49 (59.8%) women, while in Group 3 there were 12 (50%) men and 12 (50%) women. No gender difference was found between the 3 groups (p: 0.530).

The mean total hospital stay of the patients was 11.09±6.85 days in group 1, 13.76±8.62 days in group 2 and 13.46±8.45 days in group 3, and there was no statistically significant difference (p:0.187). However, when the mean length of stay in the intensive care unit was evaluated, it was 2.96±5.12 days in group 1, 3.72±4.81 days in group 2 and 6.67±7.31 days in group 3; the difference was detected (p:0.021).

When ASA scores were examined, the number of ASA I patients in group 1 was 38 (80.9%) and ASA II patients were 9 (19.1%). There was no patient with an ASA score of III. In Group 2, there were no ASA I patients, and 64 (78%) of the patients were ASA II and 18 (22%) were ASA III. When group 3 was evaluated, only 1 (4.2%) of the patients were ASA II and 23 (95.8%) were ASA III. There was a statistically significant difference in ASA scores between the groups (p:0.000) (Table 1).

In the evaluation of morbidity between groups, morbidity was not observed in 66% (n:31) of group 1, 47.6% (n:39) of group 2 and 33.3% (n:8) of group 3. The highest rate of Clavien Dindo 2 complications was seen in the groups (17% in group 1, 31.7% in group 2 and 25% in group 3). In the evaluation of complications between groups, group 3 had the highest complication rate and it was found to be statistically significant (p: 0.021).

When mortality rates were examined, 5 (10.6%) patients in group 1, 12 (14.6%) in group 2, and 10 (41.7 %) patients in group 3 died during hospitalization or within the first 30 days after discharge. These rates were evaluated as statistically significant (p:0.003).

When the causes of mortality were examined, 4 patients in group 1 died due to failure to control the pancreatic fistula, and 1 patient due to intra-abdominal sepsis developing without pancreatic fistula; In group 2, 7 patients with pancreatic fistula died, 2 patients with respiratory failure, 1 patient with bleeding, 1 patient as a result of uncontrollable biliary fistula, and 1 patient died after intra-abdominal infection that developed without pancreatic fistula that could not be controlled; In group 3, 6 patients died due to uncontrollable pancreatic fistula, 2 patients died due to respiratory failure, 1 patient died due to acute myocardial infarction, and 1 patient died after intra-abdominal infection that could not be controlled. Of the 27 patients, 17 (63%) died due to uncontrollable pancreatic fistula, 4 (14.8%) due to respiratory failure, 1 (3.7%) due to myocardial infarction, 1 (3.7%) due to aneurysmatic bleeding that could not be stopped by interventional radiology, 1 (3.7%) died due to uncontrolled biliary fistula, 2 (7.4%) died as a result of intra-abdominal infection and subsequent abdominal sepsis without fistula (Table 2).

Discussion

Pancreaticoduodenectomy surgery for pancreatic head masses has a high morbidity and mortality in the early period. In the long term, the 5-year survival is around 5% [13]. Considering the potential comorbidity risks in the elderly population, the application of this surgical procedure in the elderly population causes disagreements [14,15]. However, considering that the elderly population in the society will increase, the necessity of this surgical procedure should be investigated in the advanced elderly population [16]. In our study, we found higher rates of mortality and morbidity in the pancreaticoduodenectomy procedure in elderly patients compared to other age groups. Considering the increasing elderly population in the world, we found that surgical intervention with high comorbidities such as pancreaticoduodenectomy can be performed with higher mortality and morbidity risks compared to younger patients.

There was no statistically significant difference between the total hospital stay of the patients (p: 0.187). However, the length of stay in the intensive care unit was found to be significantly longer in the elderly patient group (p:0.021). This situation was in parallel with the increase in ASA score, which increased with age after comorbidities. However, although the length of stay in the intensive care unit was longer, no significant difference was found in the total length of stay (p: 0.187). It was determined that the hospitalization times in the service were not similar to the intensive care hospitalizations, but were shorter or the same. We think that the reason for the shorter or the same length of stay in the service and the longer length of stay in the intensive care unit may be the anxiety caused by comorbidity rather than the needs of the patients. We think that another factor affecting this situation is the long duration of intensive care unit stay before mortality in elderly patients with high mortality rate.

When early complications are evaluated according to the Clavien Dindo classification, they increase with age. This rate was 34% in the early age group, 52.4% in the middle age group and 66.7% in the elderly patient group. We think that this statistically significant (p: 0.021) situation is associated with a significant increase in the ASA score (p: 0.000) in parallel with the increase in age. In the study by Cerullo M et al., the increase in the ASA score and the increase in the incidence of gastrointestinal system surgical complications confirms this situation [17]. Like the morbidity rate, the mortality rate increases with age. Shahir MA et al. stated in their study, that this was the result of the increasing rate of comorbidity with age [18]. In our study, we found significantly higher mortality and morbidity rates in elderly patients compared to other age groups (p:0.003, p: 0.021). Andreas L. et al. evaluated the results of 722 patients and reported that pancreatic fistula was the most feared complication with a high mortality (40%) and morbidity rate [19]. In our study, we found that the most common cause of mortality and morbidity in all 3 groups was pancreatic fistula.

In the latest evaluations of the European Society of Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN, available at:https://www.nccn.org/guidelines/), which are among the international guidelines, surgical intervention is not considered as a contraindication in elderly patients. However, it has been emphasized that poor functional status may be a reason to avoid surgery. In the European Registration of Cancer Care (EURECCA) consortium guideline, it was determined that the best results would be obtained with tumor resection and chemotherapy in stage I-II pancreatic cancer patients over 70 years of age [20]. There are studies indicating that minimal inflammatory response and early-term results are positively affected in this group, which has high comorbidity with minimally invasive techniques. However, it has been recommended to be done by experienced teams [21]. In our study, we found that the stage of pancreatic cancer did not increase with age, like other parameters, and age had no effect on the stage of pancreatic cancer (p:0.592). This supports that technical difficulties of surgical procedures do not increase in elderly patients. However, the patient should be evaluated as a whole and the treatment should be individualized. V. Lopez et al. showed that advanced surgical procedures have increased mortality and morbidity in patients over 80 years of age [22], and this result was in line with our study. Considering the increase in advanced age and the number of elderly patients, this problem is growing day by day. However, we think that oncological treatments to be developed will be effective in solving this problem. However, we think that today, in advanced elderly patients with worse condition, preoperative preparation and controlling the diseases that cause comorbidity, and surgeries with high mortality and morbidity such as pancreaticoduodenectomy can be performed by experienced clinics.

This study has some limitations. First of all, the retrospective nature of the study, the small number of patients, the fact that the patients were not grouped according to their comorbidities, and the patients who were given preoperative nutritional support were not included in a separate group or excluded from the study.

Conclusion

The incidence of pancreatic cancer patients with high mortality and morbidity rates with the increase in life expectancy will increase gradually in the elderly population. In our study, we found that age further increases mortality and morbidity in pancreaticoduodenectomy surgery. We found that this situation was caused by the increase in the ASA scores of the patients with age. We think that pancreaticoduodenectomy surgery can be performed in elderly patients by considering the existing mortality and morbidities by experienced clinics after appropriate preoperative preparation.

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest
None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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